2.0 Non-Technical Abstract

Each year in the United States, over 50,000 people will be diagnosed with non-Hodgkin's lymphoma. Many patients with this disease can be cured by chemotherapy and radiation therapy. Unfortunately, most patients will develop recurrent disease, or disease that will not go away with initial treatment (primary refractory). Repeat chemotherapy in standard doses is not very effective in this setting, with only less than 10% of all patients living 5 years or longer. Encouraging results from a recent clinical trial in Italy (the PARMA trial) have shown that higher doses of chemotherapy followed by transplantation of your normal blood cells can markedly improve the long-term survival of patients with recurrent or refractory lymphoma. This trial and others have shown that this approach is now a reasonable and effective alternative for select patients. However, despite these improved results, it has become clear that high-dose chemotherapy and transplantation mostly benefits those with uncomplicated disease. Those who with more advanced disease still do not do so well. Because lymphoma is a disease that responds well to many different chemotherapy drugs, physicians have now begun to develop newer strategies that might benefit all patients, even those with high-risk disease.

One approach that could lead to an improved outcome for patients with high-risk disease involves the administration of certain drugs in the immediate post-transplant period. This idea is based on the finding that many patients whose disease returns can be found to have no lymphoma immediately after transplant. Physicians call this 'minimal residual disease'. Because most cancers are more sensitive to chemotherapy when the total amount of cancer is small, some physicians believe that any disease still present after transplant might be readily killed if the patients could receive chemotherapy at this point. Some recent clinical studies support this idea. However, because most patients - and their bone marrow - are still recovering from the transplant, physicians are concerned about giving more chemotherapy at this critical time. New approaches which could help a patients body tolerate chemotherapy at this point could improve the 'curability' of the transplant.

One such approach is based on a finding that many cancer doctors see every day. Cancer that does not go away with the initial cycles of chemotherapy tends to become resistant to future cycles of chemotherapy. Physicians call this 'acquired drug resistance'. Unfortunately, while cancer cells have the ability to become resistant, the normal cells of your body (cells in your blood, mouth and hair for example) do not have this potential, and repeat cycles of treatment end up having a greater adverse impact on your body, rather than the cancer. Over a decade ago, scientists began to believe that if they could isolate the genes that make cancer cells resistant to anti-cancer drugs, they might be able to put these genes into you bodies normal cells, making them resistant as well. When these genes are put into your blood cells, this is called 'myeloprotection'. This strategy may represent one way of reducing the newly transplanted bone marrow's vulnerability to additional chemotherapy. Recently, our laboratory and others have developed several such genes. These genes have been shown to make sensitive cells like blood cells resistant to important anti-cancer drugs. These drugs are known to be effective against lymphoma. These genes do not come from cancer cells and cannot cause new cancers. Experiments in our laboratory have shown that when we use this strategy in mice with cancer, our ability to cure these animals is greatly improved.

This pilot protocol proposes to use a virus to deliver this novel gene to the blood cells of patients undergoing transplantation for lymphoma. Following bone marrow recovery, all patients will receive increasing doses of two drugs, methotrexate and cytarabine. We will be monitoring the expression of this gene in every patient's blood, as well as their ability to tolerate this chemotherapy. We will also study the effect this approach has on the minimal residual disease. We hope this will be the first of many steps in the development of a new strategy that could help patients with lymphoma.